

### Remarks

Claims 4, 13, 14, 15, 16, 19, 20, 21, 22, and 24 are pending in this application. Claims 1-3, 5-12, 17, 18, and 23 have been cancelled. Claims 19-22 and 24 stand withdrawn. Claims 14, 15, 16, 21 and 22 have been amended in this response. No new matter has been added.

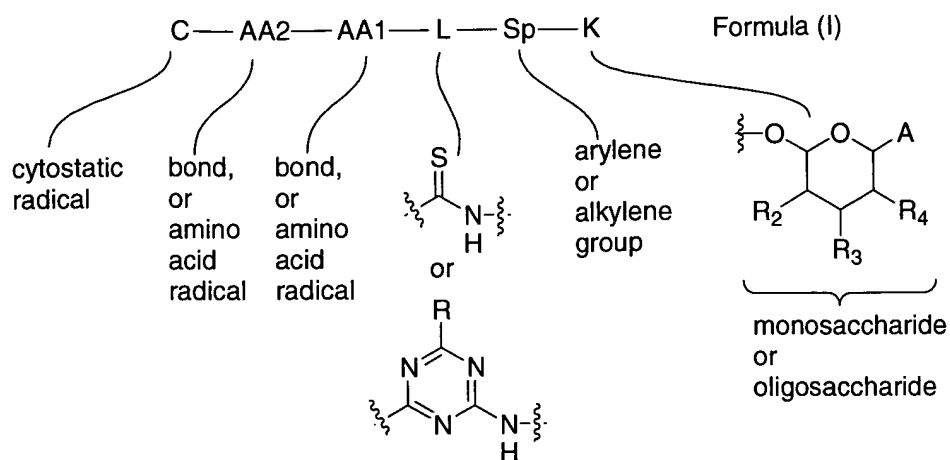
In the official action, the examiner rejected claims 4 and 13 under §112, second paragraph, on the ground that the word “addressing” in the definition of the group “IA” is vague and indefinite. This word has not been changed, because it is deemed to be appropriately used. The examiner is referred to the abstract, which states that the present invention relates to cytostatics which have a tumor-specific action as a result of linkage to an  $\alpha_v\beta_3$  integrin antagonist via preferred linking units. In other words, the IA portion of the claimed conjugates targets or “addresses” the  $\alpha_v\beta_3$  integrin receptors on cancer cells, thereby bringing the cytostatic into proximity of the cells which it is intended to act upon.

Claims 14-16 were also rejected under §112, second paragraph, on the ground that the language “characterized in that” is vague and indefinite. This language is very commonly employed in European patent applications, especially those written in Germany, and is deemed to be neither vague nor indefinite. Its meaning is the same as “wherein”. Although it is deemed unnecessary to revise this language, claims 14-16 have been amended to replace “characterized in that” with the equivalent “wherein”. This amendment should overcome the rejection.

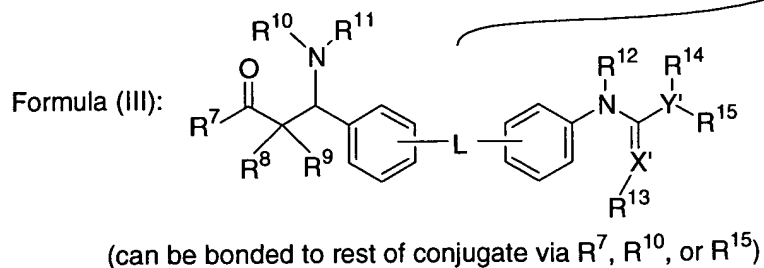
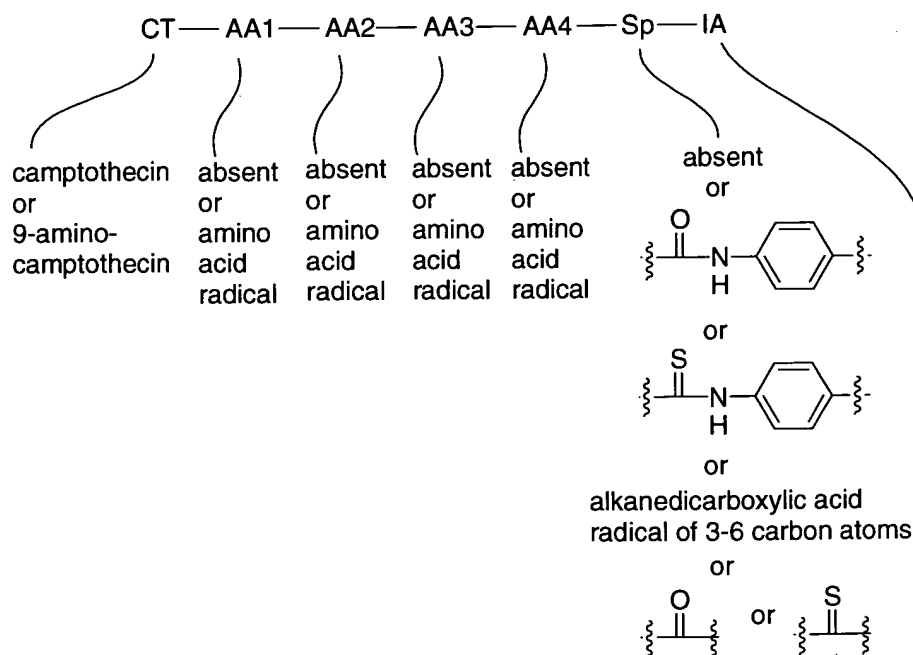
In the official action, claims 4 and 13-16 were rejected as anticipated by US patent 6,271,342 of Lerchen (Bayer AG). The cited reference does not anticipate the claims of this application.

The cited reference deals with sugar-modified cytostatics which have quite different chemical structures than the presently-claimed conjugates.

In the '342 reference, the conjugates have the general structure (I) shown below, in which the various groups are defined as illustrated below the formula (I). The examiner's attention is drawn particularly to the definition of the “K” unit, which is a sugar (in particular, a monosaccharide or oligosaccharide).



In the present application, claim 4 recites conjugates having the general formula shown below, in which the various groups are defined as illustrated below the general formula.



The examiner's attention is drawn to the fact that in contrast to the general formula (I) of the '342 reference in which the group "K" is a monosaccharide or oligosaccharide, in the present

application, the corresponding unit is an integrin antagonist “IA” which has a very different structural formula and is not a sugar.

In his rejection, the examiner states that the instant invention is drawn to a conjugate having a radical (III) where camptothecin or 9-aminocamptothecin is linked to appropriate carbohydrate units, and he refers to page 185, example 3.13 of the present application. The examiner’s conclusion that example 3.13 shows a camptothecin moiety linked to “carbohydrate units” is mistaken. “Carbohydrate” is defined by the American Heritage Dictionary as “any of a group of organic compounds that includes sugars, starches, celluloses, and gums and serves as a major energy source in the diet of animals. .... These compounds contain only carbon, hydrogen, and oxygen, usually in the ratio of 1:2:1.” Example 3.13 shows camptothecin linked to an integrin antagonist subunit of formula (III) by means of two amino acid units and an “Sp” group as defined in the present case, but there is no carbohydrate present to correspond to the “K” sugar unit of the ‘342 reference.

The examiner states that the ‘342 reference discloses glycoconjugates with camptothecin and refers to example 18 of the reference. The examiner is correct. Example 18 of the ‘342 reference shows camptothecin linked through an amino acid moiety to an “L” unit –C(S)-NH-, which is in turn linked to an “Sp” arylene (phenyl) group, which is finally connected to a terminal sugar moiety. This has no bearing on the present case, however, as the conjugates of the present application do not contain sugar moieties.

In view of this clear and significant difference between the compounds presently claimed and those of the cited reference, the cited ‘342 reference cannot anticipate the presently-claimed compounds. None of the examples shown in the cited reference falls within the scope of the present claims.

In the official action, the examiner also rejects claims 4 and 13-16 as obvious over the ‘342 reference of Lerchen. This rejection is deemed to be unfounded, as there is no suggestion in the cited reference, taken alone or together with the knowledge of one skilled in the art, that the presently-claimed conjugates should be made, or if made, that they should provide any particular desired properties or activity so as to constitute a “success” of any sort.

The examiner argues that to go from the conjugates of the ‘342 reference to the conjugates of the present application, one merely has to “adjust the particular working

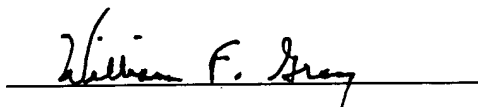
conditions”, which he states “is deemed to be merely a matter of judicious selection and routine optimization which is within the purview of the skilled artisan”. This is nonsense.

In order to derive the presently-claimed conjugates from the cited ‘342 reference, one would have to: 1) first recognize that the “L” unit –C(S)-NH- and the “Sp” unit arylene as disclosed in the ‘342 reference together correspond to the arylaminothiocarbonyl group shown as one of the possible “Sp” groups of the present application, 2) select camptothecin or 9-aminocamptothecin as the cytostatic moiety rather than employing any of the other cytostatics disclosed by the ‘342 reference, 3) determine that the chain of linking amino acid units attached to the cytostatic moiety can be up to four amino acid residues instead of a maximum of the two permitted by the disclosure of the ‘342 reference, 4) eliminate the triazine moiety from the list of possible “L” units in the conjugates of the ‘342 reference, 5) eliminate the requirement in the ‘342 reference that the conjugates must contain an “Sp” group, 6) eliminate the possibility in the ‘342 reference disclosure that the “Sp” group may be an alkylene, 7) add to the list of possible “Sp” groups the additional groups listed in the definition of “Sp” in the present application (arylaminothiocarbonyl, alkanedicarboxylic acid radical, carbonyl, and thiocarbonyl), and most importantly, 8) replace the “K” sugar unit of the ‘342 reference with the completely different integrin antagonist unit shown as formula (III) in the present claims. There is simply no suggestion to make these changes. Accordingly, the rejection on obviousness grounds is defective and should be withdrawn.

Claims 19-22 and 24 presently stand withdrawn. Claims 19, 20, and 24 relate to the process for making the compounds of claim 4. Claim 21 relates to a pharmaceutical composition containing a compound of claim 4. Claim 22 relates to a method of using a compound of claim 4 for treatment of cancer. Under the rules relating to PCT applications, unity of invention should be present with respect to claims to compounds, a process for making the compounds, and a method for using the compounds. Accordingly, applicants request that the examiner consider rejoining claims 19, 20, 24 (drawn to the process of making), and claim 22 (drawn to a method of using) once claims to conjugates are found to be patentable. In addition, applicants request that the examiner consider rejoining claim 21 (drawn to a pharmaceutical composition) when claims to the conjugates are found to be patentable, as such a claim should also be considered to satisfy the unity of invention requirements, and in addition would not require any further searching.

In view of the above amendments and arguments, the claims of this application are deemed to be in condition for allowance, and allowance is accordingly requested.

Respectfully submitted,

A handwritten signature in cursive script, reading "William F. Gray", is written over a horizontal line.

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